Complete Summary

GUIDELINE TITLE

The role of Bevacizumab (Avastin®) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of bevacizumab (Avastin) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Nov 19. 31 p. (Evidence-based series; no. 2-25). [39 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of bevacizumab (Avastin) combined with chemotherapy in the treatment of patients with advanced colorectal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Dec 12. 23 p. (Evidence-based series; no. 2-25).

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Advanced colorectal cancer (nonresectable locally advanced colorectal cancer; metastatic colorectal cancer)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether adult patients with advanced (locally advanced non-resectable or metastatic) colorectal cancer who are considered candidates for systemic therapy should receive bevacizumab (Avastin®) combined with cytotoxic chemotherapy

TARGET POPULATION

Adult patients with advanced colorectal cancer who are considered candidates for systemic therapy

INTERVENTIONS AND PRACTICES CONSIDERED

First- or second-line therapy with or without bevacizumab (Avastin®):

1. 5-Fluorouracil (5FU) plus folinic acid (leucovorin, LV, FA) (5FU/FA)
2. 5FU/FA plus irinotecan (IFL for 5FU bolus; FOLFIRI for infusional 5FU)
3. 5FU/FA plus oxaliplatin (FOLFOX)
4. Capecitabine with oxiliplatin (XELOX)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Progression-free survival
- Response rate
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Entries to MEDLINE (1996 to August 2007), EMBASE (1996 to week 37 2007), and Cochrane Library (2007, issue 3) databases and abstracts and presentations published in the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (2002 through 2007) were systematically searched for evidence relevant to this evidence-based series.

The Medical subject heading (MeSH) search terms "bevacizumab," "avastin," "colorectal neoplasms," "randomized controlled trials," "meta-analysis," "evidence-based medicine," and "review literature" were combined with the same terms used as keywords. Additional keyword search terms used were "phase 2," "phase II," and "systematic review". Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) were searched for existing evidence-based practice guidelines.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials (RCTs) that include bevacizumab (Avastin®) in the experimental arm in the treatment of adult patients with advanced colorectal cancer. These studies generally compared bevacizumab plus chemotherapy to the same chemotherapy regimen alone. Overall survival, progression-free survival, and/or response rate had to be reported.
2. Syntheses of evidence on the form of meta-analyses of RCTs and evidence-based practice guidelines.

Exclusion Criteria

The following were not considered for inclusion in this report:

1. Phase I and single-arm phase II studies.
2. Abstracts presenting preliminary or interim data only.
3. Letters and editorials.
4. Papers published in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Three phase III randomized controlled trials (RCTs) and two phase II RCTs comparing a chemotherapy regimen to the same regimen plus bevacizumab were included in this review. A pooled analysis of individual patient data from three RCTs was also included in this review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

Where possible, the data were pooled to estimate the overall effect on survival of chemotherapy with bevacizumab versus chemotherapy alone. Since hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes, these were extracted directly from the reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI) or log-rank p values. Because the analyzed trials dealt with different treatment regimens and patient groups, the assumption, necessary for fixed effects modeling, of a common treatment effect to be measured was not supportable. Therefore, a random effects model was used for all summary estimates, as it provides the more conservative estimate of effect. The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: May 2004; © 2004 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration.

Statistical heterogeneity was calculated using the chi-square (X^2) test for heterogeneity and the Higgins statistic (I^2) percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR >1.0 indicates that patients receiving chemotherapy with bevacizumab had a higher probability of experiencing death compared with chemotherapy without bevacizumab; conversely, an HR <1.0 suggests that patients receiving bevacizumab experienced a lower probability of death.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The role for bevacizumab in the management of advanced colorectal cancer was considered by the Gastrointestinal Cancer DSG. Data from randomized clinical trials involving patients with advanced colorectal cancer have consistently shown a survival advantage to the addition of bevacizumab to standard 5-fluorouracil/folinic acid (5FU/FA) based chemotherapy. For many centres in Canada, the combination of infusional 5FU/FA with irinotecan (FOLFIRI) represents the standard first-line therapy. A clinical trial of FOLFIRI with or without bevacizumab has not been performed to date. The consensus of the DSG members was that the available data supports a recommendation to extrapolate the benefit of bevacizumab when added to any 5FU based chemotherapy. This recommendation did not extend to capecitabine, as there are no published or presented trials to provide information regarding the optimal dose of this agent when combined with bevacizumab.

None of the patients included in these randomized clinical trials had received treatment with bevacizumab prior to study entry. The DSG members agreed that a recommendation could not be made regarding the continuation of bevacizumab in second-line therapy after progression on first-line therapy containing bevacizumab. The Gastrointestinal DSG will continue to update this guideline in the future, as necessary, should results of ongoing clinical trials involving bevacizumab in the treatment of advanced colorectal cancer yield new information.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Gastrointestinal Cancer Disease Site Group (DSG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC). Evidence was selected and reviewed by members of the PEBC's Gastrointestinal Cancer DSG and methodologists. This evidence-based series has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group,

which is comprised of medical, radiation, and surgical oncologists, a gastroenterologist, and two patient representatives.

External Review by Ontario Clinicians

Following review and discussion of Sections 1 and 2 of the original guideline document of this evidence-based series, the Gastrointestinal Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 of the original guideline document summarizes the draft clinical recommendations and supporting evidence developed by the panel.

Feedback was obtained through a mailed survey of medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on September 27, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The DSG reviewed the results of the survey.

This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Gastrointestinal DSG.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- For patients with advanced colorectal cancer receiving fluoropyrimidine-based chemotherapy as first-line therapy, the addition of bevacizumab is recommended to improve overall survival.
- The addition of bevacizumab to fluoropyrimidine-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not receive bevacizumab as part of their initial treatment.
- The role of continuing bevacizumab after disease progression on a bevacizumab-containing regimen is not clear due to the absence of evidence. Therefore, the continuation of bevacizumab in patients who have progressed on this therapy cannot currently be recommended outside of clinical trials.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Bevacizumab with Fluoropyrimidines Plus Irinotecan

A phase III randomized controlled trial (RCT) compared 5-fluorouracil/folinic acid (5FU/FA) with irinotecan (IFL) plus placebo to IFL combined with 5 mg/kg of bevacizumab every two weeks in patients previously untreated for advanced colorectal cancer. Patients randomized to IFL combined with bevacizumab had improved median overall survival (OS) (20.3 versus [vs.] 15.6 months; p=0.00003), median progression-free survival (PFS) (10.6 vs. 6.2 months; p<0.00001), and overall response rate (RR) (45% vs. 35%; p=0.0029) compared with IFL alone.

Bevacizumab with Fluoropyrimidines Plus Oxaliplatin

- A phase III RCT compared 5FU/FA with oxaliplatin (FOLFOX4) to FOLFOX4 plus bevacizumab in the second-line treatment of patients with advanced colorectal cancer. FOLFOX4 plus bevacizumab, 10 mg/kg every two weeks, was associated with a statistically significant increase in median overall survival (12.9 versus 10.8 months; p=0.0011) compared to FOLFOX4 alone.
- A second phase III RCT randomized untreated patients with advanced colorectal cancer to the FOLFOX4 regimen or to a combination of capecitabine and oxaliplatin (XELOX), with a second randomization to bevacizumab or placebo. This trial has been presented in abstract form only. The primary objective of this trial was met, as a statistically significant improvement in progression-free survival was demonstrated with bevacizumab over placebo (median progression-free survival: 9.4 vs. 8.0 months; hazard ratio [HR]=0.83, p=0.0023). Overall survival was prolonged in the bevacizumab arm, but this difference was not statistically significant (median overall survival: 21.3 vs. 19.9 months; HR=0.89, p=0.0769).

Bevacizumab with Fluoropyrimidines Plus Alone

Randomized phase II trials have demonstrated that 5FU/FA plus bevacizumab is associated with improved median survival, improved median time to progression (TTP), and improved response rates compared to 5FU/FA alone. When the addition to 5FU/FA of a 5 mg/kg dose of bevacizumab, given every two weeks, was compared with the addition of a 10 mg/kg dose at the same schedule, the lower dose was associated with improved outcome (median overall survival: 21.5 vs. 16.1 months; median TTP: 9.0 vs. 7.2 months; response rate 40% vs. 24%).

POTENTIAL HARMS

- In a phase III trial, 5-fluorouracil/folinic acid (5FU/FA) with irinotecan (IFL) combined with bevacizumab had comparable toxicity to IFL alone, with an increase in the incidence of grade 3 hypertension (10.9% vs. 2.3%) being the lone exception.
- The combination of 5FU/FA with oxaliplatin (FOLFOX4) plus bevacizumab was well tolerated; however, there was a statistically significant increase in grade

3 or 4 toxicity with the combination compared to FOLFOX alone (75% vs. 61%).
- The addition of bevacizumab to chemotherapy is associated with significant but manageable toxicity, specifically hypertension, bleeding, thromboembolic events, and proteinuria.

CONTRAINDICATIONS

CONTRAINDICATIONS

Bevacizumab should not be administered to patients with cerebral metastases, uncontrollable hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or those with non-healing wounds, recent surgery or trauma (i.e., within the previous 28 days), since those patients were excluded from enrolment in clinical trials using bevacizumab. The Gastrointestinal Cancer Disease Site Group considers these to be relative contraindications to the use of bevacizumab.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Data from available randomized clinical trials (RCTs) have demonstrated a significant advantage with the addition of bevacizumab to several fluoropyrimidine-based regimens, including regimens of 5-fluorouracil/folinic acid (5FU/FA), bolus 5FU/FA with irinotecan (IFL), 5FU with oxaliplatin (FOLFOX4), and capecitabine with oxaliplatin (XELOX). These studies have included regimens using 5FU given by intravenous bolus, intravenous infusional and by oral route. Survival benefit has been shown with the addition of bevacizumab to both first- and second-line chemotherapy. A reasonable conclusion is that bevacizumab in combination with any fluoropyrimidine-based chemotherapy is more effective than the same fluoropyrimidine-based chemotherapy alone.
- Given the data supporting the addition of bevacizumab to IFL and to FOLFOX, the Disease Site Group (DSG) finds the addition of bevacizumab to infusional 5FU/FA with irinotecan (FOLFIRI) reasonable, despite the fact that this combination has not been formally evaluated in an RCT. This guideline reflects previous recommendations supporting the use of FOLFIRI over IFL.
- The magnitude of incremental benefit with bevacizumab may change based on the cytotoxic chemotherapeutic regimen it is partnered with. There is insufficient evidence at present to provide any recommendations as to which chemotherapy regimen is optimal in combination with bevacizumab.
- The weight of evidence supports the use of bevacizumab with first-line chemotherapy for patients with advanced colorectal cancer. Although the evidence is less compelling for its use with second-line chemotherapy, this treatment is recommended if bevacizumab is not included in the initial treatment regimen.
- Bevacizumab should not be administered to patients with cerebral metastases, uncontrollable hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or those with non-healing wounds, recent surgery or trauma (i.e., within the previous 28 days), since

those patients were excluded from enrolment in clinical trials using bevacizumab. The Gastrointestinal Cancer DSG considers these to be relative contraindications to the use of bevacizumab.
- The addition of bevacizumab to chemotherapy is associated with significant but manageable toxicity, specifically hypertension, bleeding, thromboembolic events, and proteinuria.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of bevacizumab (Avastin) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Nov 19. 31 p. (Evidence-based series; no. 2-25). [39 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Dec 12 (revised 2007 Nov 19)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Authors of this evidence-based series were polled for conflicts of interest. No conflicts were declared.

GUIDELINE STATUS

This is the current release of the guideline.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web Site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of Bevacizumab (Avastin™) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Dec. Various p. (Practice guideline; no. 2-25). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 4, 2006. The information was verified by the guideline developer on June 1, 2006. This summary was updated by ECRI on September 29, 2006 following the FDA advisory on Avastin (bevacizumab). This summary was updated by ECRI Institute on March 28, 2008.

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